

ONE HUNDRED FOURTEENTH CONGRESS  
**Congress of the United States**  
**House of Representatives**

COMMITTEE ON ENERGY AND COMMERCE

2125 RAYBURN HOUSE OFFICE BUILDING  
WASHINGTON, DC 20515-6115

Majority (202) 225-2927  
Minority (202) 225-3641

March 29, 2016

Dr. Robert M. Califf  
Commissioner  
Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20903

Dear Dr. Califf:

Pursuant to Rules X and XI of the U.S. House of Representatives, the Committee on Energy and Commerce is examining the adequacy of the Food and Drug Administration's (FDA) strategy in combating economically-motivated adulteration<sup>1</sup> from overseas, in light of key concerns identified in the committee's investigation into the heparin contamination crisis from 2007-2008. As you may know, as part of this investigation, the committee has obtained thousands of pages of documents from the FDA, other government agencies, companies, and other sources over several years. Committee staff has also conducted numerous interviews.

This case of intentional adulteration of Chinese crude heparin, a critical drug that helps to prevent blood clots, resulted in deaths and severe reactions in American patients. However, the identities of the contaminators and how the contamination was perpetrated remain unsolved after more than seven years. In late 2007 and the first months of 2008, dozens of patients throughout the United States experienced allergic-type reactions from heparin sold by Baxter International. Several patients died and numerous patients suffered severe allergic-type reactions. Baxter heparin was soon recalled and then came off the market. The surge in the number of adverse reaction reports subsided.

Scientific evidence obtained by FDA, other authorities, researchers, and industry showed that the reactions were linked to a contaminant, overly sulfated chondroitin sulfate, or OSCS, that was intentionally introduced in China during the crude heparin manufacturing process. The

---

<sup>1</sup> One working definition of "economically-motivated adulteration" is "fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain." FDA, "Economically Motivated Adulteration: Public Meeting; Request for Comment," 74 Fed. Register 15497 (April 6, 2009).

contaminant was man-made, not a natural impurity. The FDA concluded the adulteration of heparin was an economically motivated act.<sup>2</sup> Once the contaminant was identified, the FDA and other drug-standard authorities, including U.S. Pharmacopeia, established testing methods for detecting the contaminant in heparin. The drug industry, including companies in China, adopted these testing methods to protect their heparin from this type of intentional adulteration.

Although the perpetrators' identities of the heparin contamination and their methods have remained unsolved for more than seven years, the concerns identified in the committee's investigation have broad implications for the FDA's approach to addressing economically-motivated adulteration, particularly as it relates to imported drug products from China. For heparin, FDA relies on tests to detect contaminants and more inspections to protect the U.S. heparin supply. However, even with these intensified efforts to protect heparin, serious challenges remain to significantly reduce risks for heparin from economically-motivated adulteration. For example, FDA's internal risk assessment of over 1,000 active pharmaceutical ingredients ranked heparin as "high-risk" for economic adulteration, even after instituting test methods to detect and prevent OSCS from infiltrating the U.S. heparin supply.<sup>3</sup> Moreover, according to an FDA official who was stationed in one of the FDA's field offices in China, FDA added heparin to the catalogue management program with China's State Food and Drug Administration (SFDA), which focuses on only about 10 drugs to receive enhanced oversight by SFDA at FDA's request.<sup>4</sup> Nevertheless, some of the regulatory loopholes and exemptions that permit part of the Chinese drug supply chain to operate without outside government scrutiny still remain.<sup>5</sup> In December 2015, French inspectors uncovered data suggesting that a Chinese heparin firm had manipulated tests of crude heparin that showed presence of unapproved animal source DNA, and that there was no evidence that the samples used to do the retesting came from the same batches.<sup>6</sup>

The concerns over foreign sourcing and the supply chain complexity of heparin also raise pertinent national security and biodefense issues. The U.S. Department of Health and Human Services (HHS) stated the heparin contamination story was "a clarion call to the agency, and anyone with an interest in promoting the public health, to improve the assays for testing drug and other products' ingredients, to improve controls on quality in, and to collect better information about, the supply chains of products, and to develop tools for anticipating, preventing, and

---

<sup>2</sup> U.S. Government Accountability Office (GAO), U.S. Food and Drug Administration: Response to Heparin Contamination Helped Protect Public Health; Controls That Were Needed for Working with External Entities Were Recently Added, GAO-11-95, (October 2010).

<sup>3</sup> See Memorandum from Frank W. Perrella, Sr. Staff Fellow, Div. of Mfg. & Product Quality, CDER Office of Compliance, U.S. Food & Drug Admin., to Meredith Francis, Acting Dir., Office of Drug Sec., Integrity & Recalls, CDER Office of Compliance, U.S. Food & Drug Admin., *Model Selection of APIs Vulnerable to Economically Motivated Adulteration (EMA)* (Sept. 7, 2012). In an earlier risk assessment, FDA came to the conclusion that "approximately 3% of the API's in the US market ha[d] a potential risk of adulteration by substitution." E-mail from Frank W. Perrella to Deborah Autor *et al.* (Jan. 5, 2009, 5:55 PM).

<sup>4</sup> Committee staff interview with FDA's Brenda Uratani, July 26, 2012.

<sup>5</sup> Catalog management does not apply to crude heparin suppliers as they are not regulated by SFDA. See e-mail from Brenda Uratani of FDA to Christopher Hickey and Deborah Autor, "RE: Catalog Management," September 22, 2010.

<sup>6</sup> Eric Palmer, "Potentially tainted heparin from China uncovered by French regulators," FiercePharma Manufacturing, February 29, 2016.

prosecuting *such crimes and acts of terrorism*.”<sup>7</sup> (Emphasis added). A December 2011 report from the U.S. Department of Commerce Bureau of Industry and Security’s Office of Technology Evaluation found “a very high degree of foreign sourcing and dependency” for critical healthcare components, materials and finished products supplied from countries outside the U.S., with heparin listed as one of these critical healthcare commodities. In its 2014 Report to Congress, the U.S.-China Commission noted that the growing reliance on drugs from China is “worrying” because China, by some estimates, is also the world’s leading supplier of fake and substandard drugs.<sup>8</sup> At a June 4, 2014, FDA Science Board meeting, to address shortages in the U.S. heparin supply because of vulnerabilities posed by sourcing heparin mostly from China, FDA leadership raised the issue of re-introducing bovine heparin in the U.S. market. During the meeting several board members observed that there were national security concerns with heparin sourcing. Finally, the October 2015 bipartisan report of the Blue Ribbon Study Panel on Biodefense proposed that Congress look into the origin of active pharmaceutical ingredients, and whether such foreign sourcing of critical products is creating vulnerabilities or improving U.S. ability to stockpile.

Given our interests in improving the FDA strategy to detect and prevent economically-motivated adulteration and addressing national security and biodefense implications from foreign sourcing of essential medicines, set forth below are key concerns identified during the committee’s investigation:

**1. FDA offices failed to share key important investigative information related to heparin contamination.**

An October 2011 GAO report documented instances where various FDA offices engaged in other similar enforcement or regulatory efforts on economic adulteration did not communicate or coordinate about those efforts.<sup>9</sup> The heparin case to some extent confirms this GAO finding. The two main entities engaged in investigating heparin contamination, FDA’s Office of Criminal Investigations (OCI), and FDA’s Center for Drug Evaluation and Research (CDER) Office of Compliance, communicated and exchanged some information with each other. However, with regard to sharing two key investigative leads, it appears that FDA failed to coordinate its investigations and share key investigative information in a timely manner.

First, there was a lack of sharing of information by the FDA’s OCI with the FDA’s CDER that resulted in a delay of almost four years in FDA being able to impose import alerts on Chinese firms that were shown to be the sole sources of contaminated crude heparin. The committee’s investigation found that Changzhou Scientific Protein Laboratories (CZ-SPL), the Chinese heparin API supplier to Baxter, maintained detailed traceability records for each individual crude heparin lot that could be attributed not only to the two main consolidators, but

---

<sup>7</sup> General Comments of the Department of Health and Human Services (HHS) to the Government Accountability Office’s Draft Report Entitled, “Food and Drug Administration: Response to heparin Contamination Helped Protect Public Health But More Controls Are Needed For Working With External Entities” (GAO-11-95) attached to October 15, 2010 letter from Jim R. Esquea, HHS Assistant Secretary for Legislation, to Marcia Crosse, GAO.

<sup>8</sup> 2014 Report to Congress of the U.S.-China Economic and Security Review Commission, 169 (November 2014).

<sup>9</sup> GAO, “FDA: Better Coordination Could Enhance Efforts to Address Economic Adulteration and Protect the Public Health,” GAO-12-46, October 2011 at 13.

to the individual crude heparin suppliers. Further, Baxter and Scientific Protein Laboratories (SPL), the U.S. heparin API supplier to Baxter, had individual test result information on spreadsheets indicating whether a specific lot had OSCS contamination.<sup>10</sup>

Thus, CZ-SPL had information that could trace contaminated lots back to the crude suppliers.<sup>11</sup> Although most of the crude lots were pooled from multiple suppliers into a single crude lot making attribution difficult, there were in fact a few crude lots that were not pooled and could be traced to a single crude supplier. Thus, there was evidence that could identify a presumed contaminator. In August 2008, SPL produced the lot traceability spreadsheets to FDA's OCI.<sup>12</sup> However, by that time, the OCI investigator had concluded his investigation into the contamination of the Baxter heparin and did not use the information from the spreadsheets as part of the OCI referral to the U.S. Attorney's office. Further, based on interviews and documents produced to the committee by FDA and the companies, these spreadsheets were not made available to FDA's CDER Office of Compliance.<sup>13</sup> It was not until the spring of 2012 that the FDA's CDER Office of Compliance obtained detailed traceability information from SPL, after the committee sent a letter in October 2011. Some of the sole-source Chinese heparin suppliers of contaminated heparin that FDA placed on import alert in 2012 had been used as suppliers by Chinese heparin manufacturers shipping directly to the United States during the four-year period of 2008 to 2012.

Second, FDA failed to follow-up on important foreign-government agency leads on heparin contamination. In April 2008, the FDA CDER Compliance office received documentation from a respected foreign regulatory agency<sup>14</sup> that conducted recent inspections in 2008 of two Chinese heparin firms. At the time, both these firms were still exporting to the U.S. These inspections developed important leads on the source of the OSCS.

Overall, the foreign agency inspectors identified concerns with the integrity of both firms to FDA. For example, the foreign agency inspectors reported that: (1) both heparin companies under investigation for heparin contamination admitted to an economic relationship (called "Zhuan Piao" in Chinese) that is associated with fraud. Through this relationship one heparin firm exported materials using the other company's label even if the materials were not

---

<sup>10</sup> Baxter and SPL through outside counsel provided the test results to the committee.

<sup>11</sup> Test results of crude heparin samples showed that there was already OSCS contamination in them. Thus, crude heparin lots were contaminated at the time CZ-SPL received them.

<sup>12</sup> This is based on both SPL and FDA documents produced to the committee, and written confirmation from SPL's outside counsel.

<sup>13</sup> During his interview with Committee staff on May 11, 2012, a key official with FDA's CDER Compliance was asked whether he had received traceability information on the crude heparin workshops in the SPL/CZ-SPL supply chain. The official could not remember and told staff he would need to check his files in order to provide an informed answer. In a September 6, 2012 e-mail forwarded through FDA's Office of Legislation, the official provided the following statement: "I do not recall reviewing information on who supplied starting materials in the SPL supply chain. I do recall seeing information in 2008 regarding Changzhou Techpool, Hangzhou Ruihua and Welding GMBH. These firms were crude heparin consolidators for SPL/CZ-SPL. Such firms ordinarily received crude heparin from numerous crude heparin workshops who perform initial extraction of pig mucosa and enzymatic digestion. The availability of information regarding such workshops was sparse and as a result we asked SFDA [China's FDA] to provide the information to us. I do not believe this information was ever provided by SFDA."

<sup>14</sup> Because the FDA obtained the inspection information pursuant to a confidentiality agreement with the foreign government, the committee is not naming the agency in order for FDA to continue receiving cooperation and information from this agency.

necessarily manufactured by the other company; (2) the owner and general manager of one of the heparin firms admitted to using an unregistered company in Shandong to manufacture a crude heparin (intermediate) which was at least sold to Italy; (3) the owner admitted some of the test results were not the actual results of analysis, but either “made up or calculated theoretical values”<sup>15</sup>; (4) the owner came up with an elaborate story later to show that this higher grade crude heparin was not manufactured from the factory in Shandong in the past two years, but produced in his own crude plant. However, the records reviewed had many inconsistencies such as differences in the batch numbering system and the information and signatures on the Certificates of Analysis; (5) the owner displayed an “unusual profound and extensive knowledge of the new test methodologies (for a broker)”; (6) based on the information obtained and the owner’s behavior, the inspectors believed that the Shandong factory was possibly one of the unknown API manufacturers, and the product made by the Shandong company could be of good enough quality to be sold as API but this would require additional certification and records; and (7) based on the available information and on-site inspection/observation, the inspectors believed that “[the owner] knows the identity of these unknown manufacturer(s) and the company in Shandong could be one of those ‘unknown manufacturers,’ and that “[the owner] is not a fit and proper person to supply material to” the inspectors’ home country.

While FDA used some information from this inspection for certain enforcement actions, staff found no evidence showing that the foreign agency documents or information were shared with FDA inspectors in preparation for the FDA’s inspections in 2008 of the two Chinese heparin firms in question. Further, this information was not provided to FDA’s OCI, which was conducting an open criminal investigation into heparin contamination in April 2008. The inspection reports for both firms do not reflect that the FDA inspectors were aware of the foreign agency information, and thus none of the leads developed by the foreign agency were pursued by FDA.

## **2. FDA was not responsive to credible evidence of contamination of heparin with non-porcine material before the heparin crisis, and for several years in the immediate aftermath of the crisis.**

Substituting or blending porcine heparin with bovine or animal sources of heparin raises concerns not only related to fraudulent sourcing but also for the safety and efficacy of the heparin. The World Organization on Animal Health has noted that the risk of mad cow disease in China is unknown. Further, available studies show that bovine heparin has different anti-coagulant activity than that of porcine heparin. Both FDA and industry test results confirmed long-standing practices<sup>16</sup> within the Chinese heparin industry of contaminating or adulterating crude heparin purporting to be of porcine origin with other animal sources, primarily bovine and/or ovine sources, or in combination with different animal sources. In fact, the Chinese pharmacopeia monograph for heparin sodium until 2015 actually permitted the use of

---

<sup>15</sup> The quotes are from the notes of the foreign agency inspectors.

<sup>16</sup> A confidential source provided the FDA’s OCI with HPLC (high-performance liquid chromatography) test result documents from 1997 that showed bovine heparin batches were chemically modified in order to mask its bovine origin and look like porcine heparin.

ruminant material in heparin.<sup>17</sup> Despite these concerns and test result information, FDA failed to respond to credible evidence of non-porcine contamination of the Chinese heparin supply prior to the 2008 heparin crisis. As early as 2007, industry representatives raised concerns with FDA about non-porcine heparin contamination in the Chinese heparin supply and proposed test methods to address it<sup>18</sup>, but FDA did not address this issue until 2012. In February 2012 FDA issued guidance for the heparin industry that urged the use or development of methods to identify and control the animal origin of crude heparin and confirm the species origin of heparin.<sup>19</sup> On June 26, 2013, the FDA issued guidance for industry that said manufacturers should test the heparin to determine the “species origin” to make sure the material comes only from pig intestines.<sup>20</sup>

### **3. FDA investigations and inspection strategy did not follow up on concerns about the possible recycling of OSCS-contaminated heparin.**

FDA officials and industry sources as early as 2008 suspected that massive amounts of OSCS-contaminated heparin were stockpiled in China and recycled into the heparin supply by using unapproved techniques for removing OSCS from heparin. These suspicions were voiced by credible allegations made to FDA investigators in 2008<sup>21</sup>, stated by FDA officials in internal FDA emails in 2010, and suggested by the filing of at least four different patents since 2009 by Chinese heparin firms related to the process of removing OSCS from heparin. These suspicions would also be consistent with the inexplicable trace amounts of OSCS found during FDA inspections or company audits in heparin lots made well after the 2008 crisis, and the low amounts of OSCS (2.5 percent or lower) that were explicitly permitted in the 2010 Chinese Pharmacopeia heparin sodium monograph, and then later disallowed in the 2015 Chinese Pharmacopeia heparin sodium monograph after enough time would have elapsed to have sold the recycled OSCS-contaminated heparin.

The change in the Chinese Pharmacopeia standard raises the disturbing question of whether any Chinese authorities were complicit in allowing OSCS and unapproved/undisclosed OSCS removal in the Chinese heparin supply, even after OSCS was identified and the international consensus outside of China was that the OSCS contaminant was tied to serious adverse events. Available evidence does not indicate that the FDA ever followed up on concerns about the stockpiling of OSCS-contaminated heparin, such as questioning Chinese heparin firms during inspections about this issue.

---

<sup>17</sup> Majority committee staff consulted with the staff of the U.S. Pharmacopeia regarding the English translation of the Chinese Pharmacopeia heparin monographs, and the interpretations from those translated versions.

<sup>18</sup> PCR test result information confirmed DNA from non-porcine sources in samples from different Chinese heparin firms. This information was presented to the FDA in early 2007.

<sup>19</sup> However, FDA did not specify such methods or impose any requirements. “Currently, there is no generally applicable, objective test recommended by regulators that can detect these in pharmaceutical heparin, and this continues to leave heparin exposed to contamination risks.” T.R. Rudd, E. Macchi, C. Gardini, L. Muzi, M. Guerrini, E.A. Yates, and G. Torri, “How To Find A Needle (or Anything Else) in a Haystack: Two-Dimensional Correlation Spectroscopy-Filtering with Iterative Random Sampling Applied to Pharmaceutical Heparin,” accepted by Analytical Chemistry on July 9, 2012.

<sup>20</sup> FDA, Guidance for Industry/ Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.pdf>

<sup>21</sup> These suspicions were also corroborated by internal industry emails in 2008 obtained by the committee.

**4. FDA's oversight approach to Chinese heparin firms did not fully take into account ongoing market conditions in the Chinese heparin industry.**

There is an inherent shortage in the legal pig supply in China used to make heparin, which is already vulnerable to further shortages because of disease outbreaks. Internal committee staff analysis, using yield estimates of 2,000 pigs per 1 kilogram of raw heparin,<sup>22</sup> 5000 pigs per 1 kilogram of suitable heparin for API, and 9,000 pigs per 1 kilogram of low molecular weight heparin, found that the pig supply in legal slaughterhouses in China would not be sufficient to support the number of pigs needed to manufacture the amount of Chinese heparin for export alone, not even taking into account the amount needed for the Chinese domestic heparin market.<sup>23</sup>

Internal industry documents produced to the committee help demonstrate the concern. A March 2008 internal memorandum for a company doing heparin business in China stated:

China is the largest pig-killing country in the world, with 630 million slaughters annually. Only 340 million pigs of the total are actually usable<sup>24</sup> for heparin production because they come from licensed slaughterhouses (as required by the Chinese government). Utilization of these kills for heparin production is approximately 85 percent.<sup>25</sup> While there is minimal excess capacity of licensed kills, the Chinese government has been cracking down on unlicensed slaughterers; the additional volume of pigs that were being killed at unlicensed facilities is shifting to licensed facilities and the number of licensed kills available for heparin use is expected to increase. Overall, the number of pig kills in China is expected to grow approximately 4% per year.

Using the estimates cited in the memorandum, there would be 289 million pigs available for heparin use (85 percent<sup>26</sup> of pigs obtained from regulated slaughters are usable for heparin).

---

<sup>22</sup> This estimate is based on figures cited in FDA inspection reports and internal heparin company documents.

<sup>23</sup> In fact, there is reason to believe that a substantial part of China's heparin supply may be illegally sourced. According to Li Ganjie, China's deputy minister of environmental protection, about 210 million pigs were slaughtered in 2011. Jin Zhu, "Govt to wipe out substandard slaughtering," China Daily, February 11, 2012. [http://www.chinadaily.com.cn/business/2012-02/11/content\\_14583681.htm](http://www.chinadaily.com.cn/business/2012-02/11/content_14583681.htm). However, in 2011, China exported 109 tons of heparin, which was derived from about 350 million pig intestines. See Nanjing King-Friend Biochemical Pharmaceutical Co., Response to FDA Inspection December 17-21, 2012, "Studies on Ruminant DNA Residue in Crude Heparin," at 2.

<sup>24</sup> This usability estimate (54%) is similar to an estimate presented in an article in a Chinese publication called Business Review, June 2010. "According to Hepalink's (referring to Shenzhen Hepalink, a leading Chinese heparin manufacturer) prospectus, 60% of pigs slaughtered in China are used for heparin." (Unofficial translation from Congressional Research Service).

<sup>25</sup> Chinese regulation reduced the number of qualified pig slaughterhouses from over 100,000 in 1998 to about 21,000 by 2007 (China Butchery Industry Research Report (2007-2008) at 16).

<sup>26</sup> Outside counsel for the source clarified to staff in an email that the 85% figure should be read as saying that 85% of the pigs available for heparin production provide usable heparin. This reflects a rough estimate (with a large margin of error) based on incomplete data and various factors, including the economic feasibility of collection and



There is reason to believe that this estimate may actually be overstated. According to the China Butchery Industry Research Report (2007-2008), in 2007, approximately 250 million pigs were processed in the regulated slaughterhouses.<sup>27</sup> That statistic is about 90 million lower than the 340 million estimate provided in the industry memorandum.

For the year 2007, Chinese export data<sup>28</sup> shows that 23,552 kilograms of crude heparin (multiplied by 2000 pigs per kilo) and 60,168 kilograms of pure heparin (API) (multiplied by 5,000 pigs per kilo) exported.<sup>29</sup> Using the working assumptions on yields, this would mean that Chinese heparin exports represented about 348 million pigs. Then, taking into account the working assumption provided by an industry source that the volume of the Chinese heparin market would represent about 15 percent of the amount of exports<sup>30</sup>, the estimated number of pigs available for heparin exports would be reduced to only about 246 million pigs. Even taking into account inventories built up from 2006, the analysis is not fundamentally changed because the number of 2006 slaughters was only about 8 percent higher than the number of 2007 slaughters. Thus, this analysis shows a shortfall of about 100 million pigs. Analysis conducted by staff showed similar shortfalls compared with Chinese heparin export statistics in the years that followed.

This analysis is consistent with what a knowledgeable source told an FDA criminal investigator in 2008. This source stated that if one took the amount of heparin crude received and multiplied it by the number of hogs it takes to manufacture heparin, one would quickly arrive at a number that far exceeds the capacity of the approved heparin suppliers that are claimed as the only sources of crude heparin.<sup>31</sup> This inherent shortage presents the opportunity

---

price fluctuations (e.g., when the heparin or pig casing price drops, the price of pig intestines drops too and more pig intestines become food).

<sup>27</sup> China Butchery Industry Research Report (2007-2008), Essential Genius Development Limited, at 5 (Translation from industry source). If this statistic is correct, there would not have been enough pigs available to meet export demand.

<sup>28</sup> One of the sources of the export data is a report by the Chinese drug information company Oriental Health E-Commerce Business (Beijing), renamed Health.com. "The company collects data on drug sales and prices from Chinese customs offices and is considered authoritative by Western businesspeople." Marc Kaufman, "Rise in Price Was A Sign of Trouble: Supply Problems Cause Spike That Some Say Should Have Prompted Scrutiny," The Washington Post, April 13, 2008.

<sup>29</sup> There were also 536 kilograms of low molecular weight heparin exported from China in 2007.

<sup>30</sup> This estimate has been corroborated. See Clifford S. Mintz and John Liu, "China's heparin revisited: What went wrong and has anything changed?" 19 Journal of Commercial Biotechnology 33, 38 (January 2013) ("For example, China exports 85% of its crude heparin supply, leaving only 15% for domestic use."). However, there are signs that Chinese demand could increase. "With the explosive population of cardio-cerebrovascular sufferers in China, the market share of heparin drugs keeps increasing year by year." China Pharma-Intelligence.com, "China Heparin Industry Report 2010". This trend correlates with China's aging society. The number of senior citizens over 65 in China was 104 million in 2006, and is predicted to reach 332 million in 2050. J. Hu, Y. Dai, and K. Gu, Pharmaceutical Supply Chain in China: Challenges and Opportunities, 8 (CAPS Research, March 2010). Summary of Powerpoint Presentation by Tao Jianhong, Deputy Director, of the SFDA's Southern Pharmaceuticals Economic Research Institute and Editor-in-Chief, Medicine Economic News, (2011) (translated by CRS): The domestic (Chinese) demand for heparin raw materials in 2010 was 15.9 billion units, or 60.69% of the global demand. Domestic demand is forecast to grow to 34.56 billion units in 2015, accounting for 78.02% of the global total.

<sup>31</sup> FDA, Office of Criminal Investigations Memorandum of Interview, Case No. 2008-TFM-723-0256-P, Confidential Sources, redacted month/date, 2008. Indeed, on June 5, 2012, Celsus Laboratories of Cincinnati, Ohio announced it would cease imports of crude heparin from China, in part, because "sourcing from China becomes



for fraud and illegal sourcing to make up the deficit. To the extent that diseased pigs are used, this is a public health problem because it is not known whether the purification processes in heparin manufacturing are effective against all possible animal diseases. The change in the 2015 Chinese Pharmacopeia to require 100 percent porcine heparin would seem to increase supply pressures and could incentivize more fraud and contamination by increasing the marketability of porcine heparin to include the Chinese market, and delegitimizing alternative animal sources of heparin. Knowledge about the shortages suggested by Chinese heparin statistics would have helped FDA's efforts to investigate Chinese heparin firms and the legitimacy of their supply chains. However, FDA inspection reports and internal documents produced by FDA to the committee do not indicate that FDA inspectors knew about the extent of the shortages in China's legal pig supply, and that FDA factored that into its inspections of the actual manufacturing capacities of crude heparin suppliers.

**5. FDA's lengthy open criminal investigation into an aspect of heparin contamination suggests difficulties and challenges in enforcement against criminal economic adulteration.**

The FDA has been maintaining an open criminal investigation into an aspect of heparin contamination since 2009. FDA in testimony at a February 2014 oversight hearing and in a July 2015 letter acknowledged the existence of this investigation. However, through its own investigation, the committee is aware that the investigation in question has been open for six years, which was not previously disclosed. FDA has told staff that the statute of limitations is not an impediment and this case is active. The length of time for such a case and extensive delay in this investigation seems unusual and raises serious questions about the effectiveness in investigating economically-motivated adulteration-related criminal allegations.

Because of the concerns listed above, and to assist our inquiry, we ask that you please provide the following information and documents no later than April 12, 2016:

1. What actions is FDA taking, or has taken, to improve internal communication and coordination of FDA investigative and inspection activities related to economically-motivated adulteration? Specifically, how will FDA insure information obtained by FDA's OCI is shared with other parts of FDA? Is there a protocol for the FDA's OCI to share information with other parts of FDA where the information will not be used as part of the case or the case is closed? If so, please provide the protocol. If not, why not? How will FDA insure that information obtained by foreign government agencies is provided to FDA inspectors in preparation for inspecting a foreign drug firm?
2. Given historical drug product quality problems in China, does the FDA monitor the Chinese Pharmacopeia? If so, who is responsible for doing so? Does FDA's drug inspection strategy for Chinese drug firms take into account the products that a firm makes for the Chinese domestic market? How do FDA inspectors check against cross-contamination in products for the U.S. market from products the firm makes for the Chinese market or other markets that have different product requirements? Please cite examples from FDA inspections of Chinese heparin firms

---

even more problematic since China exports significantly more than it currently claims to monitor for safety and integrity." <http://www.heparin.com/news.php>.

where this issue was covered, if any, and how FDA believes the issue of cross-contamination can be satisfactorily resolved.

3. China's recent change in its 2015 pharmacopeia not to allow any OSCS brings the position of Chinese pharmaceutical quality for heparin into alignment with FDA's position of zero tolerance for OSCS. Will the FDA reach out to its appropriate contacts in the Chinese government to find out why the Chinese government changed its position on OSCS in heparin, and whether the government would be willing to work with FDA in preventing OSCS contamination, or any other kind of contamination, in heparin? What is the Chinese government's position on the removal of OSCS from heparin and then selling heparin that has had OSCS removed? What evidence, if any, does the Chinese government have for the effectiveness of OSCS removal from heparin?
4. Did FDA investigate whether OSCS removal in heparin was taking place in China? How does FDA know that previously contaminated crude heparin from China was not recycled and imported into the U.S.? How does the FDA account in its drug inspection strategy in China for raw material shortages that could increase risks of economic adulteration and affect the integrity of drug manufacturing?
5. Please provide a list of Chinese drug firms or drug suppliers inspected by the FDA since January 1, 2013, and copies of FDA inspection reports (including all exhibits and attachments) of Chinese heparin API manufacturers or Chinese crude heparin firms for inspections conducted since January 1, 2013.
6. Do the criteria for FDA's risk assessment used for prioritizing drug inspections in China include which drugs are at highest risk of economic adulteration?
7. What have been the accomplishments of the FDA's Working Group on Economically Motivated Adulteration that first met on September 23, 2011? Who are the members of the Working Group? Has the FDA adopted a working definition of economic adulteration, as recommended by GAO? Has the FDA provided written guidance to agency centers and offices on the means to address economic adulteration, as recommended by GAO? Has the FDA received any intelligence related to EMA from the Defense Intelligence Agency (DIA)<sup>32</sup> since January 1, 2010? Has the FDA received any intelligence related to economically-motivated adulteration from any other federal agency?
8. How could FDA investigations of economically-motivated adulteration be improved?

If you have any questions regarding this request, please contact Alan Slobodin with the majority committee staff at (202) 225-2927.

---

<sup>32</sup> In April 2008 FDA reached out to DIA for any heparin-related intelligence, but was advised there was no intelligence to be shared.

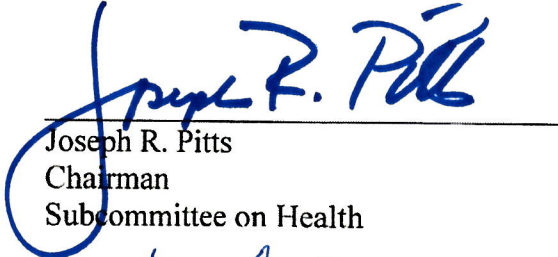
Sincerely,



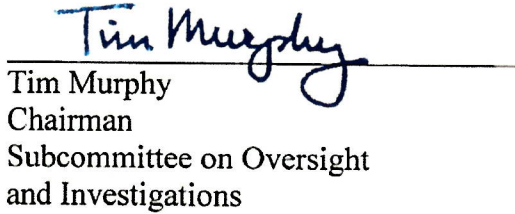
Fred Upton  
Chairman



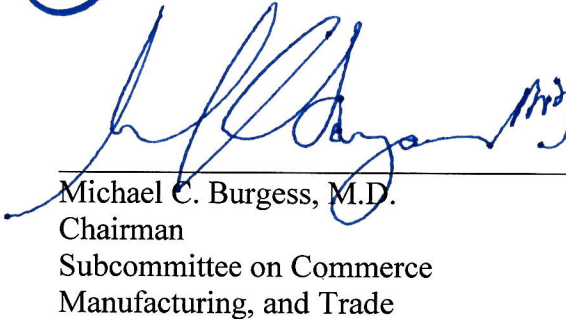
Joe Barton  
Chairman Emeritus



Joseph R. Pitts  
Chairman  
Subcommittee on Health



Tim Murphy  
Chairman  
Subcommittee on Oversight  
and Investigations



Michael C. Burgess, M.D.  
Chairman  
Subcommittee on Commerce  
Manufacturing, and Trade

cc: The Honorable Frank J. Pallone, Jr., Ranking Member  
Committee on Energy and Commerce

The Honorable Gene Green, Ranking Member  
Subcommittee on Health

The Honorable Diana DeGette, Ranking Member  
Subcommittee on Oversight and Investigations

The Honorable Jan Schakowsky, Ranking Member  
Subcommittee on Commerce, Manufacturing, and Trade